REMARKS

Applicants have amended claims 29-30, 37-38, 43-44, 51, 59-60, 67, 72-73, 80, 85-86, 95, 96 and 103. Claim 38 has been amended to correct a typographical error by replacing the word "or" with the word "of." Claims 37, 51, 67, 80, and 103 have been amended to remove the phrase "pharmaceutically acceptable." Claims 30, 44, 60, 73, 86 and 96 have been amended to replace the term "nucleotide" with "polynucleotide." Claims 29-30, 43-44, 59-60, 72-73, 85-86, and 95 have been amended to replace the term "comprising" with the phrase "fused to." Support for this amendment can be found throughout the specification as filed, for example, on page 18, line 31 through page 19, line 38 and in Example 9 on pages 46-47. Accordingly, no new matter has been added.

Claims 21-56 and 58-103 are pending.

I. Objection to Claim 38

Claim 38 has been objected to as being unclear because of a typographical error. In response, Applicants have amended the claim to replace the term "or" with the word "of," as suggested by the Examiner, thus obviating this objection. Applicants point out that this amendment merely corrects the typographical error noted by the Examiner, and does not affect the scope of the claim. Accordingly, Applicants respectfully request that this objection be reconsidered and withdrawn

II. Rejection of the Claims Under 35 U.S.C. §§ 101 and 112, First Paragraph

Claims 21-56 and 58-103 remain rejected under 35 U.S.C. § 101, because the claimed invention allegedly lacks a "credible, substantial, specific, or well established utility." *See* page 2 of Paper No. 33. These same claims also remain rejected under §112, first paragraph, for an alleged corresponding lack of enablement. Although Applicants have argued that the present invention is classified as an FK506 binding protein (FKBP) based on its possession of conserved PPIase domains present in all other FKBP's in addition to overall homology to FKBP65, the Examiner contends that:

> This is not found persuasive because Applicant has not shown that the recited proteins actually bind FK506, but only speculate the presence of this property in the polypeptides set forth as SEQ ID NO:s 6 and 8 based on sequence homology.

Paper No. 33, page 3, lines 1 through 3.

Applicants respectfully disagree and traverse. Preliminarily, Applicants point out that that the assertion that the protein of the present invention is a FKBP is based not only on sequence homology to FKBP65, but also on the following facts:

1. The proteins of the instant invention possess conserved PPIase domains present in all other FKBP's (*see* page 6 of Applicants previous response dated April 29, 2002).
2. The proteins of the instant invention possess conserved amino acid residues within each PPIase domain that are involved in FK506 binding interactions (*see* Coss *et al.*, second page, second-to-last paragraph and alignment previously submitted as Exhibit A with Applicants' response dated April 29, 2002).

Additionally, Applicants respectfully direct the Examiner's attention to the post-filing date reference Shadidy *et al.*, Biochimica et Biophysica Acta 1446:295-307 (1999), submitted herewith as Reference C7. Shadidy *et al.* disclose a member of the FKBP family, named FKBP60, which exhibits an amino acid sequence 98.8% identical to amino acid sequence of SEQ ID NO:6 as calculated by the computer program MegAlign (sequence alignment and calculation submitted herewith as Exhibit A). FKBP60 contains four PPIase domains that are nearly 100% identical to those contained within the protein of the instant invention (*see* bracketed regions in alignment, Exhibit A). Furthermore, like all FKBPs, FKBP60 has PPIase activity that is inhibited by FK506 (*see* Shadidy *et al.*, Figure 4). Shadidy *et al.* additionally identify four FK506-binding domains within murine FKBP60 that are homologous to the 87 amino acid domain defined as the FK506-binding domain in FKBP12 (*see* Shadidy et al., page 299, second column, lines 9-11, and Figure 1B). The observed PPIase activity of FKBP60 that is inhibited by FK506 further supports two of the asserted utilities of the instant invention, which are (i) binding FK506 and (ii) exhibiting PPIase activity (*see e.g.*, specification page 1, lines 13-14 and page 6, lines 38-39). Furthermore, as taught by the specification at page 6, lines 29-31, one skilled in the art would find it more likely than not that the protein of the instant invention, as a member of the FKBP family of proteins, would be useful in the treatment of diseases caused by an over-active immune system. For example, antibodies to this protein could be useful in treating disorders such as graft vs. host disease, rheumatoid arthritis, and inflammation.

Additionally, the Examiner contends that:

> However, even if said polypeptides bind FK506 and are in fact a member of the FKBP family, the function or utility will not have been established.

Paper No. 33, page 3.

In response, Applicants respectfully disagree, and maintain that, as discussed in Applicants' response of February 11, 2003, the FKBP's are a distinct class of highly conserved intracellular receptors termed immunophilins with well-established functions. These functions include:

1. binding to FK506 or rapamycin;
2. immunosuppressant activity upon binding to FK506 or rapamycin; and
3. peptidylprolyl *cis-trans*-isomerase (PPIase) activity that is inhibited upon binding to FK506 or rapamycin.

See Coss *et al.*, submitted as Exhibit C with Applicants' response dated April 29, 2002, and references cited therein. Coss *et al.* does not in any way question the ability of FKBPs to bind FK506 (one asserted utility of the instant invention), nor does it dispute the fact that FKBPs confer immunosuppressive effects upon binding FK506. This reference additionally confirms the well-known PPIase activity of this family of proteins, stating "A characteristic shared by immunophilins is peptidylprolyl cis-trans-isomerase (PPIase) activity, which is inhibited upon drug binding." *See* Coss *et al.*, page 29336, second column, lines 6-9. While the second-to-last paragraph of Coss *et al.* does recite the phrase "functional diversity of the FKBP family members," this diversity refers to the different subcellular localizations of the various FKBPs and their associations with different protein complexes. This statement does not imply that some FKBPs bind FK506 while others do not (indeed, FKBP stands for FK506-binding protein), or that some FKBPs exhibit PPIase activity, while others do not. In fact, these authors state in the first column of page 29340 that FKBP65 "has PPIase activity with kinetics similar to other FKBPs."

The Examiner has noted that the inhibition of PPIase activity and the immunosuppressive activity of FKBPs are two separate functions of the proteins, both related to FK506 binding (*see* Paper No.33, page 3, last paragraph). As described on page 1, lines 25-29 of the specification, PPIase activity of the FKBPs is inhibited upon FK506 binding, while the immunosuppressive activity of FKBPs is initiated upon FK506 binding. However, this does not change the fact that the FKBPs are a family of proteins possessing

both of these well-established functions. The Examiner adds that "in view of the potential diverse intracellular interactions, one could envisage multiple functions for said proteins." As noted above, one of skill in the art would expect this protein, as a member of the FKBP family, to exhibit the well known functions of all other FKBPs, *i.e.*, exhibiting PPIase activity, binding to FK506 and eliciting immunosuppressive effects upon said binding. Additional functions, even if present, do not detract from the previously disclosed utilities for the claimed invention.

The Examiner further asserts that the specification "does not disclose that said binding of said instantly claimed proteins to FK506 leads to immunosuppression by inhibiting T cell proliferation and or differentiation." Applicants submit that the mechanism by which FK506 binding to FKBPs leads to immunosuppression was well established in the art at the time of filing (*see* Coss et al., first paragraph), and therefore need not be described in the specification. As stated in § 2164.05(a) of the M.P.E.P., "The specification need not disclose what is well known to those skilled in the art and preferably omits that which is well-known to those skilled and already available to the public." *See In re Buchner*, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991); *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986), *cert. denied*, 480 U.S. 947 (1987); and *Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co.*, 730 F.2d 1452, 1463, 221 USPQ 481, 489 (Fed. Cir. 1984). Further, Applicants respectfully submit that a description of the mechanism of function or how the claimed invention exerts its immunosuppressive effect is unnecessary. Indeed, it is well established that an applicant is not required to set forth the mechanisms through which the invention functions, nor is the applicant required to even know how or why an invention works. *Se,e e.g.*, *Newman v. Quigg*, 11 U.S.P.Q.2d 1340, 1345 (Fed. Cir. 1989); *Diamond Rubber Co. v. Consolidated Rubber Tire Co.*, 220 U.S. 428, 435-36, 55 L. Ed. 527, 31 S. Ct. 444 (1911); *Fromson v. Advance Offset Plate Inc.*, 720 F.2d 1565, 1570, 219 U.S.P.Q. (BNA) 1137, 1140 (Fed. Cir. 1983).

In light of the above, Applicants submit that the above rejection under 35 U.S.C. §101 have been overcome. Accordingly, Applicants respectfully request that this rejection be reconsidered and withdrawn.

The Examiner has also rejected the claims under 35 U.S.C. § 112, first paragraph, for alleged lack of enablement. In view of the reasons discussed above in response to the rejection under 35 U.S.C. § 101, the claimed invention is supported by a credible, specific,

and substantial utility. The Examiner "should not impose a 35 U.S.C. § 112, first paragraph, rejection grounded on a 'lack of utility' basis unless a 35 U.S.C. § 101 rejection is proper." M.P.E.P. § 2107(IV). Therefore, since the claimed invention complies with the utility requirements of 35 U.S.C. § 101, Applicants respectfully request that the rejection under 35 U.S.C. § 112, first paragraph, be reconsidered and withdrawn.

III. Rejections Under 35 U.S.C. § 112, First Paragraph

A. Written Description

Claims 29-30, 43-45, 72-74, 85-87, 59-61, and 95-97 have been rejected for allegedly lacking written description in the specification as filed. In particular, the Examiner contends that:

> The instant claims are drawn to a nucleic acid molecule that is heterologous to SEQ ID NO:5 or 7, or a nucleic acid molecule that encodes a polypeptide that is heterologous to SEQ ID NO:6 or 8. However, the instant specification discloses no heterologous sequences of said nucleic acid molecules or polypeptides, other than said sequences which are all from homo sapiens. Therefore, the invention encompassing heterologous sequences such as those from other species is not adequately described.
>
> Paper No. 33, page 4, section (A).

Applicants respectfully disagree, and maintain that the previously pending claims fully complied with 35 U.S.C. §112, first paragraph. However, claims 29, 43, 59, 72, 85 and 95 have been amended to replace the term "comprising" with the phrase "fused to." As disclosed on page 18, line 31 through page 19, line 38 and in Example 9 on pages 46-47, the specification clearly describes examples of such heterologous sequences, including heterologous signal sequences, functional regions, regions of charged amino acids (to improve stability and persistence during purification from the host cell), marker sequences such as hexa-histidine or hemagglutinin, albumin, nuclear localization signals, or parts of the constant domain of immunoglobulins (IgG). Since the claims as amended clearly comply with 35 U.S.C. §112, first paragraph, Applicants respectfully request that the rejection be reconsidered and withdrawn.

B. Enablement

Claims 37, 51, 67, 80 and 103 have been rejected for allegedly lacking enablement in the specification. In particular, the Examiner contends that:

> [I]t would require undue experimentation to predict which diseases could be treated using a pharmaceutical composition comprising the recited nucleic acid.
>
> Paper No. 33, page 4, section (B).

Applicants respectfully disagree, and maintain that the previously pending claims fully complied with 35 U.S.C. §112, first paragraph. However, claims 37, 51, 67, 80 and 103 have been amended to delete the phrase "pharmaceutically acceptable," thereby rendering this rejection moot. Accordingly, Applicants respectfully request that this rejection be reconsidered and withdrawn.

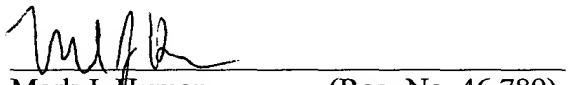
CONCLUSION

In view of the foregoing, Applicants believe that this application is now in condition for allowance, and an early notice to that effect is urged. The Examiner is invited to call the undersigned at the phone number provided below if any further action by Applicants would expedite the issuance of this application, or to schedule an interview as requested above.

If there are any fees due in connection with the filing of this paper, please charge the fees to our Deposit Account No. 08-3425. If a fee is required for an extension of time under 37 C.F.R. § 1.136, such an extension is requested and the appropriate fee should also be charged to our Deposit Account.

Respectfully submitted,

Dated: August 4, 2003



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MMW/MJH/JMM/KM/lrc

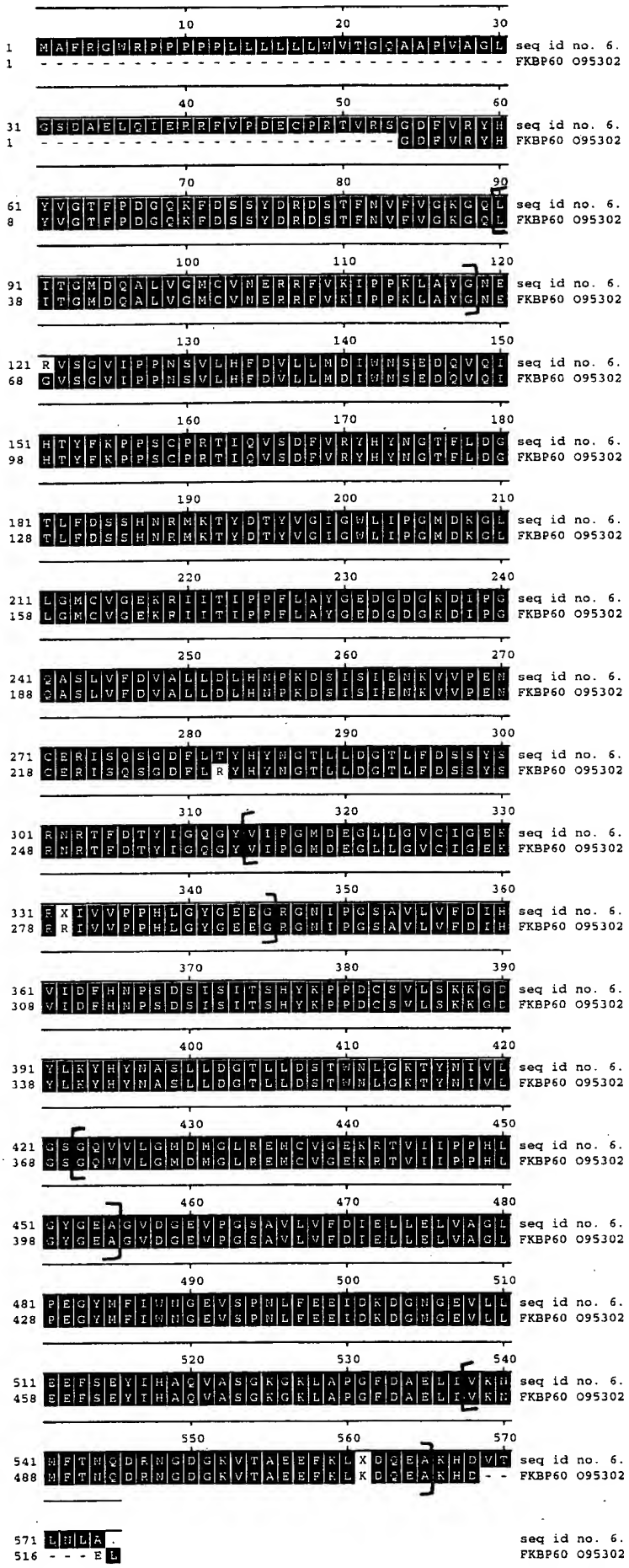
EXHIBIT A

[ ] = PPIase domain I →

[ ] = PPIase domain II →

[ ] = PPIase domain III →

[ ] = PPIase domain IV →



Decoration 'Decoration #1': Shade (with solid black) residues that match th
Consensus exactly.

Sequence pair distances of Untitled, using Clustal method with PAM250 residue weight table.
Friday, July 11, 2003 11:30 AM

Percent Identity

Divergence

	1	2	
1		98.8	1
2	0.6		2
	1	2	

seq id no. 6.PRO

FKBP60 O95302.PRO